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Editor - Captain F. W. Farrar, MC, USN

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A Laboratory and Clinical Investigation of Dihydrostreptomycin: Dihydrostreptomycin is an antibacterial agent which has been prepared by catalytic hydrogenation of streptomycin. It differs from the latter structurally only in having a hydroxyl instead of a carbonyl group in the streptobiosamine portion of the molecule. The dihydro derivative has been reported to be slightly less toxic than streptomycin as measured by the LD_{50} in mice, and the two compounds are active against the same micro-organisms in vitro. There are quantitative differences in the antibacterial effectiveness of the two compounds, the dihydro derivative being slightly less active against most strains. Donovick and Rake observed that strains of Hemophilus influenzae which were resistant to streptomycin were also resistant to dihydrostreptomycin, and this finding has been confirmed on resistant strains of other species in this laboratory. These early reports did not suggest any advantage of dihydrostreptomycin over the parent compound for clinical use, unless the derivative were significantly different in its distribution or toxicity.

Certain of the toxic reactions observed during the administration of streptomycin to human beings were not previously disclosed by routine toxicity tests in animals. Examples of these include several manifestations of hypersensitivity such as fever, skin eruptions, asthma, and eosinophilia, which may be encountered during prolonged treatment with streptomycin. Occasionally, these reactions of hypersensitivity have been so severe that therapy has had to be abandoned or interrupted for many weeks. An even more severe limitation on the usefulness of streptomycin results from its involvement of vestibular and auditory functions.

It is generally recognized that slight changes in chemical composition may alter the capacity of a drug to give rise to manifestations of hypersensitivity. Dihydrostreptomycin, with a greatly altered polar group, might be expected to differ significantly from streptomycin in this regard. It is also recognized that other manifestations of toxicity may be altered by such slight chemical changes. A striking example of such alteration has been reported by Schmidt, who found that the introduction of a single hydroxyl group into the side chain of 6-methoxy derivatives of 8-aminoquinolines reduced their specific neurotoxicity by 75 percent.

It seemed possible, therefore, that dihydrostreptomycin might be different from streptomycin in its toxicity for human beings despite the similarity of the two drugs in other respects. Accordingly, in March 1947, a laboratory and clinical investigation of dihydrostreptomycin was started and the results observed form the basis for the present report. The greater portion of the study was planned to determine (1) if dihydrostreptomycin were toxic, (2) how its toxicity compared with that of streptomycin, and (3) what its relative therapeutic effectiveness might be.

It appeared that, insofar as tested, the pharmacologic and antibacterial characteristics of dihydrostreptomycin and streptomycin are qualitatively similar but that certain quantitative differences between the two compounds may be of importance. Virtually all of the important toxic reactions produced by streptomycin can be produced by the dihydro derivative. Thus, in the larger dosages employed in this study, dihydrostreptomycin caused vestibular dysfunction, hearing loss, renal damage, and eosinophilia. Dihydrostreptomycin, however, seems to be distinctly less neurotoxic than streptomycin, as judged by the length of therapy and the total dose of each required to produce the "dizziness" characteristic of vestibular dysfunction. This symptom usually has been the first evidence of vestibular dysfunction in patients receiving large doses of streptomycin. In earlier studies, it was observed that 37 of 38 patients being treated for ninety days with 3.0 Gm. of streptomycin daily, given in eight intramuscular injections, dizziness was experienced about the twentieth day of treatment when a total of about 60 Gm. had been given. In contrast, dihydrostreptomycin produced "dizziness" first on the forty-second day after a total of 176 Gm., and in other patients on the forty-fourth and sixty-first days after total amounts of 195 and 270 Gm., respectively. It should be noted, however, that in 2 patients who never were dizzy from a total amount of 166 Gm. for one and 96 Gm. for the other, the caloric response was absent on the thirty-second and thirty-third days. The dose of dihydrostreptomycin ranged from 18 to 110 mg. per kg. of body weight per day. It was occasionally necessary to reduce the daily dose or to discontinue treatment for a few days when the injections of "crude" dihydrostreptomycin became too painful or when the supply was temporarily exhausted.

It thus appears that neurotoxicity, as indicated by the symptoms and signs of vestibular dysfunction, is manifested later and after a larger total dose with 5.0 Gm. of dihydrostreptomycin daily than with 3.0 Gm. of streptomycin daily.

Dihydrostreptomycin also can produce damage to the auditory apparatus similar to the toxic effect of streptomycin. Although a comparison of the toxicity of the two compounds on the auditory apparatus is difficult, the observations thus far indicate that dihydrostreptomycin is no more toxic and may prove to be significantly less toxic in this respect than streptomycin.

Renal damage, which has been observed in patients receiving streptomycin also occurred in those getting dihydrostreptomycin. The three patients in this study who showed renal damage had received very large doses of the crude preparation. It is worthy of note that, in addition to the active drug, these patients received large doses of impurities, the renal toxicity of which is not known. No evidence of renal dysfunction has been observed with 3.0 Gm. or less of dihydrostreptomycin daily.

Although the local reactions at the site of injection of the crude preparations of dihydrostreptomycin were frequently severe, the purified preparations used

in this study have not caused local reactions. In view of the lower neurotoxicity of dihydrostreptomycin, it will be of particular interest to determine whether the purified preparations of dihydrostreptomycin are any less toxic than streptomycin when given intrathecally.

In addition to the quantitative differences between dihydrostreptomycin and streptomycin, at least one qualitative difference was noted. Five patients with readily demonstrable hypersensitivity to streptomycin tolerated dihydrostreptomycin in dosage as high as 2.0 Gm. daily without untoward reaction. Dihydrostreptomycin should be useful, therefore, in the few patients in whom this type of reaction develops when interruption of treatment is undesirable.

In twelve cases of pulmonary tuberculosis, the therapeutic results were judged to be as good as those that have been obtained with streptomycin. Resistant strains of Mycobacterium tuberculosis have emerged during treatment with dihydrostreptomycin in the same fashion as with streptomycin. Highly resistant strains, not inhibited by 1,000 micrograms per c.c. of one compound, are similarly resistant to the other compound.

It should be emphasized that, although the toxicity of streptomycin is well known, there is as yet little information on the therapeutic effectiveness in humans of streptomycin in very low dosage. Hence, the precise relation of toxic dose to optimal therapeutic dose of streptomycin has not yet been established. It is thus of considerable importance that experience be gained on the therapeutic effectiveness of dihydrostreptomycin in dosages which are well tolerated for prolonged periods.

Dihydrostreptomycin should prove to be useful in the treatment of patients unable to tolerate streptomycin because of hypersensitivity. The lower neurotoxicity of the dihydro derivative also suggests that it is preferable to streptomycin for the treatment of patients who require large doses or long courses of the antibacterial agent. (Am. Rev. Tuberc., Nov. '48 - L. B. Hobson et al.)

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An Experimental Evaluation of Dihydrostreptomycin: The present studies show that the antibacterial efficacy of dihydrostreptomycin against Mycobacterium tuberculosis is equal to that of streptomycin, but its neurotoxic action in animals is significantly less than that of the parent substance.

Three samples of crystalline dihydrostreptomycin and two of crystalline streptomycin calcium chloride complex were used in this investigation. Dihydrostreptomycin and streptomycin showed closely comparable activity on a weight basis against M. tuberculosis of both human (H37Rv) and avian types in vitro. In vivo, they were equally effective against avian tuberculosis in chicks. Details of these studies will be reported elsewhere. No substantial differences were

observed in mice infected with Klebsiella pneumoniae, Diplococcus pneumoniae I-37, Staphlococcus aureus SM or Eberthella typhosa. Cultures of M. tuberculosis, resistant to streptomycin, were also resistant to dihydrostreptomycin. Mice infected with streptomycin-resistant cultures of Salmonella schottmülleri could not be protected by either streptomycin or dihydrostreptomycin.

The toxic actions of dihydrostreptomycin and streptomycin on the nervous system were compared in cats. It was apparent that at all of the dose levels which produced intoxication, the onset of ataxia was longer delayed with dihydrostreptomycin than with streptomycin. Neither streptomycin in a dose of 25 mg. per kg., nor dihydrostreptomycin in a dose of 38 mg. per kg., produced any ataxia or other sign of vestibular disturbance during periods of treatment lasting 122 and 111 days, respectively. In larger doses dihydrostreptomycin produced vestibular disturbance in all animals tested, but its onset was significantly delayed as compared with that caused by streptomycin.

In the animals receiving doses of 200 mg. per kg. a more intensive study of the vestibular defect was made by electrical recording of nystagmus, a procedure which permitted a quantitative evaluation of the loss of response occasioned by the drug. It was apparent that loss of nystagmus, like ataxia, occurs earlier in the course of treatment with streptomycin than with equivalent doses of dihydrostreptomycin. In only one cat was the loss of nystagmus after 30 days of treatment with dihydrostreptomycin as great as it was in all 4 cats of the other groups after 20 days of treatment with streptomycin. The test with streptomycin was stopped after 20 days because the intoxication was so severe that the cats were rapidly losing weight. In contrast, the animals treated with dihydrostreptomycin maintained or gained weight during the 30-day treatment.

Two dogs treated with streptomycin, in doses of 200 mg. per kg. daily, showed an ataxic gait on the twelfth and fourteenth days, respectively, but 2 dogs receiving equal doses of dihydrostreptomycin showed no evidence of a neurotoxic effect during 18 days of treatment.

Biochemical, hematological, and pathological studies revealed no significant evidence of other toxicity in dogs or monkeys treated with dihydrostreptomycin.

Dihydrostreptomycin and streptomycin appear to affect the nervous system in the same fashion. No qualitative distinctions have been noted in cats, the signs produced by the two drugs differing only in time of onset and in severity. Whether these quantitative differences in toxicity depend upon less rapid excretion of streptomycin or more ready access to the nervous system, or upon differences in metabolism of the two substances, cannot be answered at present. The significant fact is that, in the conversion of streptomycin to dihydrostreptomycin, the neurotoxic action has been reduced without sacrificing the antibacterial efficacy. The two properties do not, therefore, appear to be indissolubly linked and presumably do not depend upon the same molecular configuration. (Am. Rev. Tuberc., Nov. '48 - A. O. Edison et al.)

The Distribution of Dihydrostreptomycin in Various Body Fluids: In contrast to streptomycin, the usual doses of dihydrostreptomycin have not caused vertigo to develop. In order to determine if the absence of symptoms of neurotoxicity was due to low concentrations of the drug, the concentrations of dihydrostreptomycin in the blood and other body fluids were studied.

The determinations were performed by a modification of the cup-plate method of assay. The test organism used was the SM strain of Staphylococcus aureus. The drug was always given intramuscularly in a concentration of 0.2 Gm. per c.c. of distilled water.

After the intramuscular administration of dihydrostreptomycin, the drug was rapidly absorbrd into the blood, the greatest concentration being reached in about one hour. Significant quantities of the drug were present in the blood for twenty-four hours after the intramuscular administration of 1.0 or 2.0 Gm. The drug passed through the placental membrane and was found in the fetal blood. Dihydrostreptomycin was found in significant quantities in the pleural fluid and in the cerebrospinal fluid of patients who had received the drug by intramuscular injection. The drug was excreted in large amounts in the urine, 70 percent or more of the daily dose being present in each twenty-four hour sample. The absorption, distribution, and excretion of streptomycin and dihydrostreptomycin are very similar. Absence of symptoms of neurotoxicity after intramuscular administration of dihydrostreptomycin cannot be attributed to low concentration of the drug in the blood. (Am. Rev. Tuberc., Nov. '48 - L. Levin et al.)

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The Clinical Administration of Dihydrostreptomycin in Tuberculosis: When streptomycin was developed in 1944, it was found to be less toxic and more effective than promin or any of the other antituberculosis drugs. It now has become recognized as an indispensable aid to the medical and surgical treatment of many types of tuberculosis.

Two principal handicaps to more widespread utilization of streptomycin in tuberculosis have appeared, namely, (1) the frequent emergence of streptomycin-resistant strains of Mycobacterium tuberculosis, and (2) toxic manifestations produced by streptomycin which frequently are uncomfortable and at times are severe and disabling.

Neurotoxic manifestations of streptomycin therapy are almost uniformly observed in patients when doses of 40 mg. or more per kg. of body weight per day are administered for a few weeks. These reactions were described in the first reports concerning streptomycin therapy in clinical tuberculosis. Most prominent among these toxic reactions is the damage to the vestibular function of the eighth cranial nerve. When the daily dose of streptomycin is reduced to

less than 20 mg. per kg. of body weight, these symptoms are observed in only a minority of patients treated, but it is not always possible to predict which patients will be affected. Many physicians believe that these lower dosage ranges are equally effective in the treatment of tuberculosis, especially those types of tuberculous disease which respond most promptly to specific therapy. It has not been demonstrated conclusively, however, that these lower dosage levels are adequate to meet some clinical situations in which the patient would be benefited by larger doses. Furthermore, many physicians have expressed the need for a drug with a wider margin of safety than is offered by streptomycin.

Accordingly, at the Mayo Clinic, an investigation to determine the clinical possibilities of dihydrostreptomycin was undertaken early in 1948, after the effectiveness of the drug against experimental tuberculosis had been demonstrated during the previous year in this institution. Although the number of patients treated remains small, the results have been sufficiently uniform to justify the publication of this preliminary report and to indicate that dihydrostreptomycin possesses certain advantages over streptomycin for the treatment of tuberculosis.

Dihydrostreptomycin was administered to 14 patients, 13 of whom were suffering from tuberculosis of various types. Severe nerve damage developed in only one patient; and mild symptoms of vestibular dysfunction occurred in another. In no other case did any subjective or objective evidence of nerve damage develop. Moreover, in no case did any evidence of allergic response to dihydrostreptomycin develop. If similar doses of streptomycin had been administered, it is believed that in most of these cases symptoms of drug toxicity would have developed. The dihydrostreptomycin utilized in these studies was of a purified type which the manufacturers stated was comparable in purity to present-day commercial streptomycin.

The results of this study showed that dihydrostreptomycin is an effective drug for the treatment of some types of clinical tuberculosis. Its activity is probably similar to that of streptomycin but it is clearly much less toxic than streptomycin when given in comparable doses for similar periods. Most significant is the fact that dihydrostreptomycin may be administered to patients in doses of from 2.0 to 3.0 Gm. per day for sixty days, or perhaps longer, with little danger of producing impairment of function of the organs of equilibration.

The fact that dihydrostreptomycin may be administered to some patients who are markedly allergic to streptomycin and the fact that eosinophilia has not been observed in this series of treated patients may be important.

The only unfavorable attribute of dihydrostreptomycin which was noted was irritation of the tissues at the site of injection. The irritation is appreciably more severe than that produced by streptomycin. Intrathecal injection of dihydrostreptomycin is not recommended for the treatment of meningitis unless a less irritant form of the drug can be produced. Patients with meningitis treated with dihydrostreptomycin might be given purified streptomycin intrathecally.

The series of patients reported on here is not sufficiently large, nor is the period of observation sufficiently long, to have revealed all of the possible toxic potentialities of dihydrostreptomycin. (Am. Rev. Tuberc., Nov. '48 - H. C. Hinshaw et al.)

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A New Treatment in Obliterative Diseases of Peripheral Arteries: In recent preliminary studies on the treatment of chronic obliterative peripheral arterial diseases in which radioactive sodium was utilized to measure changes in circulation, it has been found that the intra-arterial infusion of a dilute solution of histamine could produce benefits similar to the immediate effects of sympathectomy and could be repeated when new developments made it necessary. This article concerns the use of histamine in the femoral artery in patients with a severe insufficiency of the peripheral arterial circulation of their lower extremities caused by an endarteritis obliterans due to thromboangiitis or arteriosclerosis.

It was necessary to introduce the solution at a higher pressure than the diastolic pressure in the artery. In order to overcome the pressure in the femoral artery the infusion bottle was prepared in the following manner. The ordinary 500-c.c. infusion burette was capped by a stopper with two holes which was held down tightly with several strips of adhesive tape. Through one opening in the stopper, a piece of glass tubing was inserted reaching above the histamine solution. The outer end of this tube which contained an air filter was connected by means of a Y tube to the manometer and cuff of the ordinary blood pressure apparatus. The arm cuff was rolled up snugly and held with a stout elastic band. Thus, with a closed circuit established, positive pressure could be created in the inverted infusion bottle and the pressure at any time would be registered on the manometer.

With the skin and subcutaneous tissue anesthetized with procaine, a two-inch, 20-gauge needle was introduced into the femoral artery. To date, well over 500 arterial punctures have been made, and at no time have any local intra- or extra-arterial complications resulted.

The bright red blood and its pulsating thrust into a Kaufman syringe attached to the needle were evidence of entry into the artery. The pressure was then raised or lowered until the pulsating blood could be seen only during each systole of the heart. The solution consisted of 500 c.c. of normal saline to which was added between 1.38 and 2.75 mg. of histamine acid phosphate equivalent respectively to 0.5 mg. and 1.0 mg. of histamine base. Generally, the infusion was given weekly. The flow rate was measured by observing the drip indicator during the diastolic fall in pressure during which flow into the artery took place. It was found that between two and five drops per heart beat permitted an erythema of the thigh to develop without any subjective symptoms. An asymptomatic flush of the face was found to be of little importance.

The immediate objective responses to an intra-arterial infusion of histamine are striking. The degree and extent of these reactions are obviously dependent upon the extent of the arterial block and the availability of a collateral circulation. The effects include a change in the color of the skin, its temperature, a distention of the superficial veins, and alteration in the rate of diffusion of radioactive sodium. As the solution of histamine begins to enter the femoral artery, a definite erythema spreads over the thigh from the groin and buttock to the knee, becoming more intense as the treatment continues. The back of the leg, then the front, and last, the foot, become pink. The extent of the spread is variable, and patterns appearing on the extremity in pink and white suggest the location and degree of block in the larger vessels. The pale areas may become diffused later if the collateral vessels are dilated by the histamine. If the infusion is given too rapidly, thus permitting histamine to escape into the general circulation, erythema is observed to develop in the upper half of the body and the leg becomes only mottled and the foot even cyanotic. However, when the flow is slowed, permitting fixation of the histamine in the leg, then the skin of the leg and foot becomes pink and the rest of the body remains pale. Such an observation is corroborative evidence of the futility of giving vasodilators intravenously. With such use, the generalized dispersal of the vasodilator opens the more sensitive and healthy arteries of the upper half of the body first. Their dilatation diverts blood from the arteries of the lower half because total blood volume is essentially fixed in amount. When this occurs, such use is not only without value but it may actually be dangerous. This undesirable effect of misplaced vasodilatation has been observed after high sympathectomy when vasodilatation in the lower abdomen was so extensive that it diverted blood from the foot and precipitated gangrene. Usually, a rise in skin temperature follows the erythema rapidly in the thigh, more slowly in the foot. Many patients show a rise of 6° C. and some show none in the toes. A rise in the temperature of the skin over the calf muscles has been increased to such a degree that it might be expected that relief of the pains experienced by patients while walking and sleeping would result. The diffusion of radiosodium made after an infusion is accelerated (an occurrence indicating increased blood flow) has been noted consistently over the calf muscles but not over the foot. This is to be expected because the block is more severe and collateral vessels are less numerous in the foot than in the calf. The superficial veins invariably become distended even though the horizontal position is maintained. The oscillometric readings in the patients studied were all very low, as expected, because none had palpable popliteal pulsations. Their amplitude never increased after single or multiple infusions of histamine. When a patient has a palpable pulse, the amplitude after a single infusion may rise as much as 25 percent. These immediate and variable manifestations of vasodilatation after a single infusion will be later correlated with the cumulative effects of repeated infusions on walking, and sleep tolerance, reduced by obliterative disease.

No other treatment was used concurrently in the present study. Suggestion as a factor in improvement is ruled out by the fact that each patient had previously

been subjected to one or more types of treatment and attendant encouragement for from nine months to five years.

In evaluating the efficacy of histamine treatment, two symptoms related to arterial insufficiency in the lower extremities were chosen. The first was the number of blocks the patient was able to walk before he was forced to stop by pain in the calf of his leg. The second was sleep tolerance which represents the number of hours the patient could lie in bed in a horizontal position before he was awakened by pain in his calf muscles and forced to get out of bed for relief.

Treatments were given weekly until the walking tolerance was increased to 10 blocks. Then one treatment a month was given until a tolerance of from 18 to 20 blocks was attained when treatment ceased. If a recession occurred, therapy was resumed until the desired level was again reached. Patients whose response to treatment was of this character were placed in the "very good" group. The response was considered to be only "good" when walking tolerance increased to between six and 10 blocks and reached a plateau. When this stage was reached the interval between treatments was also lengthened without permitting a relapse. The response was called "poor" when no or negligible improvement was noted after six treatments. The effects on walking tolerance developed in response to histamine therapy were "very good" in 51 percent, "good" in 33 percent, and "poor" in 16 percent. The effect of treatment on sleep pain was completely successful, for which patients were most grateful. The improvement in walking and sleep tolerance was prompt, occurring after from three to six weekly treatments.

The results produced by multiple infusions of histamine can be correlated with the immediate effects induced by a single infusion. Patterns may be established which could be used in estimating the amount and availability of the collateral circulation and the probability of its responding to this form of treatment.

It has been shown that histamine given by arterial infusion is a powerful dilator of all the components of the peripheral vascular system. Its increase of the temperature of the skin and radiosodium diffusion indicates that the arteries, large and small, are widened. The erythema which follows its use means that the precapillary sphincters are relaxed and the minute vessels are wide open. The superficial veins become visibly dilated. These physiological responses are probably as short lived as six hours. Still, as the results show, cumulative and mounting improvement follows weekly infusion. Therefore, it is reasonable to inquire why such an enduring and competent circulation should develop after histamine. An analysis of the problem in full perspective may yield the answer. To begin with, in each patient a primary influence, such as smoking, or a degenerative process initiates a block in one or more arteries. The arterial collaterals, though available, do not take over

the burden because they are thrown into a reflex spasm as a result of the original block and its attendant distress. In some, they open spontaneously in six weeks. In the group of patients treated with histamine this had not occurred when they were first seen.

From the benefit in walking and sleep tolerance obtained by about 85 percent of the patients, it is apparent that their arterial blood flow is now effective and competent. In theory there are two ways in which histamine could bring this about. First, it could come about in the manner shown by Clarke and Clarke in their experiment on the rabbit, that under acute stimuli arteriovenous anastomoses developed from thread-like capillaries to five times their original size. Evidence for such violent vasodilating properties was presented in the results which follow a single histamine infusion. Their repetition should be able to develop arteriovenous anastomoses in great numbers. The second reason may be found in evidence which shows that the reversal of vasospasm following histamine will persist when there is no reflex extravascular cause for vasospasm. Pain can render histamine or a sympathectomy inert as a vasodilator, permitting at most only temporary effectiveness. The clinical results on patients H. S. and T. M. are the basis for this impression. The walking and sleep tolerance of H. S. increased and his radiosodium diffusion in the calf rose after histamine, but when his toe was accidentally crushed, then histamine and later a lumbar sympathectomy failed to help him. The latter was followed three days later by a drop in radiosodium diffusion. Similarly, T. M. first showed a drop in radiosodium diffusion indicating no vasodilatation following a histamine infusion. After his pain due to an infection and an ingrown toe nail was relieved, the same type of infusion was able to bring about a rise in radiosodium diffusion.

Fear has also been shown to be a cause of vasospasm. A recent experience gave confirmation of this phenomenon. A marked rubor was developing during an infusion of histamine into the femoral artery of a patient with scleroderma when it suddenly faded completely from her foot after the patient began discussing the details of the death of a close relative. In less than two minutes after the conversation was terminated, with the arterial infusion still running, the pallor was replaced by a bright erythema. Dread fear had again completely reversed the dilatation caused by histamine. It follows, then, that the crux of the success of histamine therapy rests not alone on the presence and availability of a collateral circulation which it can activate, but also on the absence of a continuing cause for a histamine-resistant reflex vasospasm of these same collaterals. The patterns established in response to a single arterial infusion of histamine are not, as the results show, sharply delineated for each classification of response to therapy. However, when these are correlated with all the variables, vascular and extravascular, it is possible to grade the extent of the occlusion and the probability of circumventing it with histamine given by artery. (Ann. Int. Med., Nov. '48 - I. Mufson)

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Report of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction: Because the uniformly favorable results in small numbers of cases appeared to justify a more extensive study of the use of anticoagulants in the treatment of coronary thrombosis, the Board of Directors of the American Heart Association, in the spring of 1946, authorized the formation of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction. This committee is composed of internists with special interest in cardiovascular diseases who are associated with the sixteen hospitals which have contributed cases to this study. Workers in several additional institutions have participated in an advisory or consulting capacity.

Under the conditions of this investigation, 1,000 patients with coronary occlusion and myocardial infarction have been studied. Slightly fewer than one half of these 1,000 patients have been treated by conventional methods of therapy alone. The others have been treated with anticoagulants, in addition to conventional methods. The present report includes data obtained from analysis of the first 800 cases reported. Although it is possible that the addition of the last 200 cases, and other later revisions, may change the figures somewhat, it is unlikely that the conclusions will be altered significantly, since the relationship of the control and treated groups concerning deaths and thrombo-embolic complications has remained relatively stable as the sample has increased in size.

Three hundred sixty-eight patients admitted to the participating services on even days received conventional therapy and constitute "the control group." Four hundred thirty-two patients admitted on odd days received anticoagulants in addition to conventional therapy and constitute "the treated group."

The principles used in this study as guides in the administration of dicoumarol and heparin are as follows:

a. Heparin may be given for the first 48 hours or more, if desired.
b. Prothrombin determinations are to be done each day and no dicoumarol should ever be ordered unless the morning prothrombin report is available.
c. Dicoumarol, from 200 to 300 mg. daily, should be given until the prothrombin time is 30 seconds.
d. Dicoumarol, from 50 to 100 mg. daily, should be given if the prothrombin time is between 30 and 35 seconds.
e. Dicoumarol is withheld if the prothrombin time is 35 seconds or more. Then, no drug is given until the prothrombin time is again down to 30 seconds or less, after which the drug is again given cautiously in 100-mg. doses.
f. The Link-Shapiro technic, using undiluted whole plasma, or the Quick method is to be used for determining the prothrombin clotting time, and it is suggested that the Link-Shapiro method, using 12.5 percent diluted plasma, be employed as an additional check or safeguard. All prothrombin times are given in terms of the Link-Shapiro (undiluted) method.

g. Unless contraindications arise, the dicoumarol therapy is to be continued in the chosen cases over a minimum period of 30 days; preferably 30 days after the last thrombo-embolic episode.

h. In instances of hemorrhagic manifestations, the use of synthetic vitamin K preparations in doses of from 60 to 75 mg. and transfusions of fresh whole blood, which may be citrated, are recommended.

A comparison of the patients in the "control" group with those in the "treated" group shows a striking similarity with regard to age, history of previous infarction, and estimated severity of the present attack, as shown in Table I below. The average age of men in the control group was 58.9 years,

TABLE I. COMPOSITION OF SAMPLE. TOTAL GROUP: 800 CASES OF CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION SURVIVING FIRST DAY OF HOSPITALIZATION

ITEM CQMPARED	CONTROL GROUP (EVEN DAYS)	TREATED GROUP (ODD DAYS)
Number of cases	368	432
Average age	60 years	59 years
Proportion males	77%	76%
One or more previous infarctions	24%	22%
Illness "severe" at onset	23%	30%
Anticoagulant therapy received (exceptions as noted)	88% no anticoagulants 12% some anticoagulants (primarily after complications)	81% Dicumarol without heparin 14% Dicumarol plus some heparin 3% no anticoagulants because of renal or liver disease or hemorrhage 2% no anticoagulants because of miscellaneous errors

and in the treated group, 57.2 years. The average age of women in the control group was 64.1 years, and in the treated group, 64.6 years. In this series of 800 cases, the average age of female patients was approximately 6.4 years greater than that of male patients.

The rates of deaths and the number of thrombo-embolic complications per 100 cases have been calculated for the control and treated groups as a whole, by week of illness, by age of patient, and by type and location of the specific thrombo-embolic complication. The percentage of patients in whom one or more complications developed has also been analyzed. The results in every category studied indicate that the use of anticoagulants improves strikingly the outlook of the patient suffering coronary occlusion with myocardial infarction.

The incidence of hemorrhagic manifestations was also analyzed. It was found that about six minor or moderate hemorrhagic manifestations per 100 cases occur in patients not receiving anticoagulants; the incidence in patients receiving anticoagulants was about 12 per hundred.

Although the minimum prolongation of the prothrombin time necessary to obtain a therapeutic effect from dicoumarol in each patient has not been established, it is the authors' experience that a range of from 30 to 50 seconds, as measured by the Link-Shapiro modification of the Quick one-stage technic, indicates a safe and an effective therapeutic level. This range of prothrombin times approximates a decrease in prothrombin activity to between 20 and 10 percent as determined in the Central Laboratory, used in this study. In using heparin, an attempt is made to prolong the clotting time of whole blood to approximately three times the normal value by the Lee-White technic. In only four cases of the entire series did thrombo-embolic complications occur when the prothrombin time had been maintained at a level of 30 seconds or above for at least three days prior to the occurrence of the complication.

On the basis of the data compiled from 800 cases of coronary occlusion with myocardial infarction, it is concluded that:

1. Patients treated with anticoagulant therapy in addition to the conventional forms of therapy experience a death rate and incidence of thrombo-embolic complications during the first six-week period following an attack which are markedly lower than those experienced by patients treated solely by conventional methods.

2. Anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless a definite contraindication exists.

3. In the absence of other hemorrhagic states, the hazards from hemorrhage due to anticoagulants are not sufficient to contraindicate their use in the treatment of coronary occlusion providing there are facilities for adequate laboratory and clinical control. (Am. Heart J., Dec. '48 - I. S. Wright et al.)

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Nitrogen Balance: Within the past decade more and more attention has been given to the nutritional deficiencies of surgical patients. It is now generally recognized that the patient whose nutritional deficiencies have been, in large part, corrected prior to operation will withstand anesthesia and operation better than one who is not so prepared. However, there is no unanimity of opinion regarding the methods best calculated to correct nutritional deficiencies.

The study of the nutritional deficiencies in man has, in large part, centered around the protein imbalance. It may well be that such intensive studies in a single direction have been correct, but all clinicians interested in this field must constantly remind themselves that nutritional deficiencies in man are usually of a complex nature.

One reads that "the metabolic needs of the patient have been met by the administration of 3,000 c.c. of a five percent solution of glucose every twenty-four

hours;" that amount of glucose provides but 600 calories a day, approximately one third of the energy requirements of a patient at rest in bed. Regardless of the statement that the total calories in the diet are not very important, anyone who has studied the problem of undernutrition knows that the total caloric intake is important.

Time and again within the past five years, it has been stated that the protein requirements of the patient have been met because for short periods the patient has been "in positive nitrogen balance." This statement may, in reality, mean very little, for a positive nitrogen balance does not indicate positively that the nitrogen made available to the patient has been utilized to restore the depleted stores of tissue and plasma protein. Determinations of plasma protein concentration may mean very little under such circumstances, for these provide no concrete data which reflect the increase or decrease of the total plasma protein.

Certain of the substances being used to reinforce depleted protein stores are only slowly metabolized in the body following intravenous injection. Gelatin and serum albumin are conspicuous agents of this type and yet one is asked to believe that they, too, rapidly play a part in correcting a protein deficiency, while in reality they are stored for relatively long periods in the body before they become available for utilization in a nutritional sense.

A positive nitrogen balance means only that more nitrogen has been retained in the body on a given intake than has been excreted. It should not be made to imply that deficiencies in a nutritional sense have been corrected. If utilization of the tools of the biochemist is to be continued, how to use them and how properly to interpret the results, which the studies provide, must be learned. (Surgery, Dec. '48 - Editorial, I. S. Ravdin)

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Lumbar Puncture Headache: After puncture of the spinal theca, whether for diagnostic aspiration of cerebrospinal fluid or for spinal anesthesia, it is not uncommon for a very characteristic headache to develop. Pain may be more or less generalized over the calvarium but is often especially severe at the back of the head and may spread into the neck, shoulders or back. The neck may feel stiff and sustained contraction of the posterior cervical muscles (neck rigidity) is common. But the feature which is quite invariable and which distinguishes this headache from all others is its reaction to change of posture, its very striking exacerbation when the patient sits up, and its relief when the patient lies down. The headache may begin from a few hours to a few days after lumbar puncture, and it usually lasts twenty-four hours or more.

McRobert (1918) suggested that this headache was due to the leakage of c.s.f. from the hole made by the needle. Leakage of fluid after lumbar puncture

was demonstrated by Ingvar in a patient with tuberculous meningitis, by Heldt (1929), Nelson (1930), and Merrit and Fremont-Smith (1938). That this leakage was the cause of headache was first demonstrated by Jacobaeus and Frumerie (1923) who found in two cases that lumbar puncture during the headache showed a spinal pressure of less than 1.5 cm. in one and about atmospheric in the other. The pressure was restored to 10 cm. by injecting 50 c.c. saline in the first and 35 c.c. in the second, headache being relieved in each instance. Nelson recorded 3 further cases in which there were pressures of 13, 15, and 18 cm. at the first lumbar puncture and 2.5, 2.0, and 5.5 cm. at the second lumbar puncture. Kunkle, Ray and Wolff (1943) and the author (1939) have each recorded one further case in which lumbar puncture revealed fluid pressure somewhat or greatly reduced, and in which restoration of pressure relieved the headache. A low c.s.f. pressure in patients with lumbar-puncture headache has also been described by Alpers (1925) and Solomon (1924).

The author has now examined 11 cases, in 7 of which spinal pressure has been measured. These are the subject of this paper.

When a patient with lumbar-puncture headache is again tapped while in the horizontal position, the moment of piercing the spinal theca is appreciated by the characteristic feel of the needle, but no fluid emerges. To demonstrate that the subarachnoid space has actually been entered it is necessary to attach a syringe and withdraw fluid. If a manometer is now connected in the ordinary way no fluid rises in it, and to measure the pressure it is necessary to attach to the needle a saline-filled rubber tube terminating in a small glass tube. In this way it was found that in 6 of the 7 cases of post-puncture headache, cerebrospinal fluid pressure was at or about zero. In the seventh case it was higher, 80 mm. c.s.f. For restoring the pressures to normal, warm sterile physiological saline was injected. In the 6 cases with very low initial pressures the volume of saline needed to restore normal pressure was of the order of from 30 to 50 c.c.; in the seventh case rather less. In each of these 7 cases, restoring the pressure in this way abolished headache, if it was present in the horizontal posture, and prevented its occurrence on sitting up. The relief in most cases was temporary, the headache returning in from one half to two hours, no doubt owing to continued leak through the hole in the theca.

In these cases, headache was usually increased by compression of the jugular veins in the neck, and by shaking the head. Not infrequently the headache throbbed with the pulse and in about half the cases was relieved by compression of the carotid artery in the neck.

It seems then that the primary cause of headache is diminution in the volume of c.s.f. in the subarachnoid space and that the deficit is of the order of from 30 to 50 c.c.

Lumbar-puncture headache can be ascribed to caudad displacement of the base and posterior parts of the brain with tension on the anchoring structures,

particularly the tissues around the large arteries at the base. (Brain, Sept. '48 - G. W. Pickering)

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Further Note on Dibenamine in Shock Prevention: The 17 December 1948 issue of the Medical News Letter (page 18) contained material on the Protective Action of Dibenamine After Hemorrhage and After Muscle Trauma which was taken from an article in the October 1948 issue of the Proceedings of the Society of Experimental Biology and Medicine.

The November 1948 issue of the Proceedings of the Society of Experimental Biology and Medicine contains the following:

> In Article 16647P, October 1948, p. 150, the Dibenamine used was received in January 1947. On comparison with a newly obtained lot, the older material contained only 1/3 to 1/4 its original strength. The dosage therefore stated in the article was too large by the corresponding amount.

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Aureomycin in Treatment of Pneumococcal Pneumonia and Meningococcemia: Aureomycin is active in vitro and in experimental animals against Gram-positive and Gram-negative bacteria and is also effective against experimental infections with rickettsias and with viruses of the psittacosis lymphogranuloma venereum group. The findings in 4 cases of pneumococcal pneumonia and in one case of meningococcemia are presented here briefly. The bacteriologic methods are described elsewhere.

The cases of lobar pneumonia were of moderate severity and a single lobe was involved in each instance. All were in males ranging in age from 16 to 65 years. Pneumococci were identified and typed from the sputum in each instance and from the blood in one case before oral aureomycin therapy was started. One patient received an initial dose of 0.5 Gm. followed by 0.25 Gm. every 6 hours for a total of 5 Gm.; the others received 0.5 Gm. every 6 or 8 hours for a total of 10 Gm. in 2 cases and 20 Gm. in the oldest patient.

Both subjective and objective improvement, and a return to normal temperature occurred in each case between 18 and 36 hours after the first dose (the oldest patient who had the severest illness and jaundice showed the slowest response). The number of pneumococci decreased rapidly in the sputum following treatment and none could be demonstrated by any of the available methods, including mouse inoculation, after the second day of treatment. The pneumococci were completely inhibited by aureomycin in concentrations of from 0.25 to 3.0 micrograms per ml.

A tentative diagnosis of Rocky Mountain spotted fever was first made in the case of meningococcemia on the basis of a history of tick bites, high fever, headache, slightly stiff neck and a rapidly spreading maculopapular eruption involving the trunk and extremities. Lumbar puncture yielded normal spinal fluid. Treatment was begun 12 hours after the onset of symptoms. The patient received 4 doses of 0.5 Gm. followed by 4 doses of 0.35 Gm. and then 3 doses of 0.25 Gm., at 6-hour intervals. The patient was afebrile and much improved symptomatically, and the rash had almost cleared within 18 hours after the first dose. A blood culture obtained before treatment was started yielded a group I meningococcus, and subsequent blood cultures were negative.

The results in these cases appear to be comparable with those obtained in similar cases treated with penicillin or with the sulfonamides. There were no toxic effects attributable to aureomycin in any of these cases.

Further experience is needed to determine the optimum dosage and duration of treatment as well as the effect in more severe cases. It is considered that further clinical trial of aureomycin in these and other types of infections is warranted. (Proc. Soc. Exper. Biol. and Med., Nov. '48 - H. S. Collins et al.)

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Carbon Tetrachloride Poisoning: Ten patients have been admitted to the U. S. Marine Hospital, Seattle, Washington, since 1937, with carbon tetrachloride poisoning; of these, four patients died. The occurrence of most of the cases could have been prevented by exercising the precaution of proper ventilation.

Carbon tetrachloride is one of the most widely used of the organic solvents. It is employed as a dry cleaning fluid, a metal degreaser, rubber solvent, fire extinguishing agent, household cleaner, and for a variety of other industrial and nonindustrial applications. Numerous cases of poisoning have been reported in the literature, but the reported cases probably are only a small fraction of the actual number of cases that have occurred. In most instances, fatal poisoning has occurred from the isolated or individual use of carbon tetrachloride as contrasted with its use in industry.

Toxic reactions to carbon tetrachloride may result from a single brief exposure to a high concentration of the vapor, from prolonged or repeated exposure to a moderately high concentration or from regular daily exposure to lower concentrations; also from repeated contact with the skin or from ingestion. Obese persons, alcoholics, undernourished individuals, and those with diabetes, peptic ulcer, or disease of the liver, kidney, lungs, or heart are likely to be especially susceptible to carbon tetrachloride injury.

The signs and symptoms of carbon tetrachloride poisoning differ somewhat according to the nature of exposure.

Acute intoxication produced from a single exposure to a high concentration results in mental confusion, feeling of fullness in the head, headache, dizziness, nausea, stupor, or loss of consciousness. Death from respiratory failure may occur. There may be a delayed appearance of systemic poisoning, with liver and kidney symptoms.

Repeated or prolonged inhalation may cause headache, fatigue, nausea, vomiting, dizziness, visual disturbances, and bleeding from the mucous membranes followed by severe acute nephritis and toxic hepatitis. It may be injurious to the central nervous system.

Some cases are caused by the ingestion of carbon tetrachloride and result in nausea, vomiting, abdominal distress, diarrhea, bloody stools, and coma followed by hepatitis, jaundice, and nephritis.

The general clinical picture is headache, nausea, vomiting, hematemesis, hematuria, icterus, oliguria, and retention of urine. Pulmonary complications may occur as late as a week after exposure. Although experimental proof is lacking, it is felt that carbon tetrachloride is removed from the body by the expired air as well as by the kidneys. Some may be detoxified by the liver.

It is stated that anuria and oliguria are often the primary physiological disturbances in man, and the development of pulmonary edema is often the immediate cause of death.

One of the 10 case histories reported was that of a 30-year-old merchant seaman who was admitted on 21 June 1947, complaining of nausea, vomiting, malaise, and headaches. He stated that he had become mildly intoxicated on 18 June 1947. The following day he spent 2 hours cleaning clothes with carbon tetrachloride in a poorly ventilated room. He had a history of moderate drinking. The urine contained albumin, casts, and red blood cells. The blood urea nitrogen was 95 mg. percent. The blood creatinine was 7.2 mg. percent. The diagnosis was acute nephritis due to carbon tetrachloride poisoning. The patient recovered and was discharged on 17 July 1947.

Alcohol seemed to be a predisposing factor in eight of the ten cases. Seven of the patients presented severe kidney damage. Anuria and pulmonary edema were the most serious clinical phenomena and were the chief causes of death in the four fatal cases. In most of these cases the users of the carbon tetrachloride were not aware of its danger, and apparently the operators of the ships or industries were not aware of the danger involved in its use. In all of these cases improper ventilation was a factor.

The main purpose of this article is to emphasize the frequent and preventable occurrence of carbon tetrachloride poisoning. It is felt that ship operators and small business concerns are improperly educated as to the dangers of carbon

tetrachloride. Carbon tetrachloride should be properly labeled with instructions explaining the dangers in its use. It should always be used in a properly ventilated room. It is believed that investigation will show that these precautions are not being observed. (Pub. Health Reps., 10 Dec. '48 - G. A. Abbott and M. J. Miller)

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Testicular Degeneration as a Result of Infra-Red and Microwave Irradiation: The mammalian scrotum has been established as being a local thermoregulator for the testes. Moore and Quick found the scrotal temperature of white rats to be from 2° to 8° C. lower than the temperature of the abdominal cavity. A subabdominal temperature in the scrotum has been shown to be necessary for the continuance of spermatogenesis. Moore confined the testes of guinea pigs in the abdominal cavity for varying periods of time and found that an abdominal retention of seven days resulted in a complete disorganization of the germinal epithelium of the seminiferous tubules. He considered the cause of this degeneration to be due to the higher temperature of the abdominal cavity.

It was the purpose of this study to determine the effect of 12-cm. electromagnetic radiations on testicular tissue. In addition, attempts were made to confirm the results of previous investigators concerning the effects of infra-red irradiations on testes.

Male albino rats of the Sprague-Dawley strain, ranging in age from 120 to 200 days were employed. A Raytheon Microtherm generator (model CMD4) which produced a wavelength of approximately 12 cm. was used to apply the high frequency radiations. A variac was provided by means of which the power output was regulated. The corner type reflector was used. The infra-red source rated at 600 watts was of the nonluminous type, and a 9-inch hemispherical reflector was employed. In all cases irradiation was applied to the testis through the scrotum.

The results of experiments with 12-cm. electromagnetic irradiations showed that in all cases when the testicular temperature was raised to 35° C. or higher there was evidence of damage to testicular tissue. At temperatures of from 31° to 35° C. approximately 50 percent of the testes showed signs of degenerative changes. The testes of animals exposed to 30° C. were not affected.

The results of experiments with infra-red irradiation showed that testes from 67 percent of the animals exposed to 43° C. were damaged. Testicular degeneration was not found when the temperature of the testes was maintained at 38° C. for 10 minutes by infra-red rays. No damage was found in the testes of control animals.

Testicular degeneration resulting from exposures to microwaves and infra-red irradiations presented a similar histologic appearance which was typical of the degeneration seen in experimental cryptorchidism.

The temperatures at which damage was noted from infra-red irradiations were approximately from 3° to 5° C. lower than those reported by Moore and Chase. These investigators placed the bulb of a thermometer close to the scrotum to register the degree of heat applied. With the needle-thermocouple method of temperature measurement used in the experiments reported here it was possible to register the temperature within the testes.

Following electromagnetic irradiation testicular degeneration was found at temperatures below those at which damage occurred from infra-red irradiations. All of the testes which were elevated to a temperature level of 35° C. and above with microwaves were found to contain degenerated tubules.

The outcome of this experiment clearly shows that testicular damage will result from 12-cm. irradiations at a temperature below that of the abdominal cavity and below that necessary to cause injury by infra-red exposures. This finding suggests that damage may result in part from factors other than heat. However, it should be pointed out that measurements of temperature were made only near the center of the testes and the possibility exists that areas adjacent to the field of irradiation may have been subjected to temperatures somewhat in excess of those recorded.

These findings suggest that precautions should be taken by those working in the field of high frequency electromagnetic generators and by those giving treatments with microwave generators. Because of the unusual susceptibility of testicular tissue to increased temperatures, it seems desirable to shield the testes from high frequency electromagnetic waves during periods of treatment or exposure. (Proc. Soc. Exper. Biol. and Med., Nov. '48 - C. J. Imig et al.)

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The Detection of Barbituric Acid Derivatives in Urine: In all patients admitted to a hospital in coma it is important to consider the possibility of acute barbiturate intoxication. Without a history of ingestion of barbiturate the diagnosis is difficult; the physical examination may be of little value, except to indicate a severe central nervous system depression. Under these conditions a positive diagnosis cannot be made without recovering and identifying barbiturate in the urine, blood, or stomach contents.

The quickest possible answer to the question whether any barbituric acid derivative at all is present is more important than a determination of the absolute amount and the kind of substituted barbituric acid. It is true that certain barbiturates appear in the urine even when taken in therapeutic quantities, but this is limited to barbital (from 60 to 80 percent elimination by the kidneys) and phenobarbital (from 20 to 30 percent elimination) whereas the other, shorter-acting barbiturates are nearly completely destroyed by the liver. Therefore, these barbiturates may not appear in the urines, even if toxic amounts have been ingested or injected.

With a strongly positive qualitative test for barbiturate in the urine, there is strong presumptive evidence for the conclusion that the coma is due to barbiturate intoxication.

The method of the author and co-workers for detecting barbituric acid derivatives in the urine utilizes a modification of the cobalt color reaction which differs from methods previously described in the following respects: (1) ether is used as the solvent instead of chloroform; (2) a wetting agent is employed to break up any emulsion formed between urine and the solvent; (3) activated charcoal is used as a decolorizer; (4) the method emphasizes speed and simplicity rather than strict quantitative precision.

Acidify 100 ml. of urine to pH 4.0 (nitrazine paper) with dilute sulfuric acid (one volume concentrated acid to six volumes of water). In a separatory funnel extract twice with 75 ml. portions of absolute ether (must be free from peroxides which interfere with development of the final blue color), shaking for 30 seconds during each extraction. If an emulsion forms which will not separate on standing, add a suitable wetting agent (1 Gm. or more of "Dreft," Proctor and Gamble Co., Cincinnati, Ohio), rotate the funnel gently and wait for the layers to separate. Combine the ether extracts in a 250 ml. Erlenmeyer flask. Add activated charcoal (Nuchar C-250, 2 Gm.) and anhydrous sodium sulfate (5 Gm.) and shake vigorously for one minute. Allow to stand for three minutes, then decant the clear ether solution through filter paper, collecting the filtrate in a separatory funnel. Wash the activated charcoal-sodium sulfate residue with 25 ml. of absolute ether and transfer the entire mixture to the filter paper. Evaporate the filtrate to from 25 to 50 ml. on the steam bath, allowing the solution to drain from the separatory funnel into a 100-ml. beaker. Finally, evaporate to 2 ml. in a suitably calibrated tube.

To the final 2 ml. of concentrated ether extract add 0.5 percent lithium hydroxide in absolute methanol (5 drops or 0.2 ml.). If more than 1 mg. of barbituric acid is present a white precipitate will form. Add, drop by drop, 0.2 percent cobaltous acetate in absolute methanol until any blue-violet color reaches its maximum intensity (do not exceed 10 drops or 0.4 ml.). A distinct blue-violet color as compared with a control test carried out on 2 ml. of absolute ether indicates the presence of a barbituric acid derivative in the original urine sample. A rich green color indicates the presence of a thiobarbiturate such as Pentothal sodium.

It is possible that a certain amount of barbiturate may be adsorbed by the charcoal. This would reduce the sensitivity of the procedure to some extent but, it is felt, would not seriously limit the usefulness of the method.

The characteristic blue-violet color is produced with as little as 0.2 mg. of barbital, phenobarbital, or pentobarbital (in 2 ml. of absolute ether). This is considered the practical limit of sensitivity of the cobalt color test as carried out in the author's method.

The method described can be carried out in about one hour. (Am. J. Clin. Path., Nov. '48 - R. W. Merley)

Protection of Dental X-Ray Technicians from Irradiation: The National Committee on Radiation Protection has recently concluded, on the basis of extensive research, that 0.3 r (roentgen units) per week, either in a single or cumulative dose, should be established as the permissible dosage for persons working around x-ray apparatus.

This means that it will be necessary to employ a more rigid standard of precaution than has been observed heretofore. The recommended procedure, based on a survey conducted in August 1948 at the Naval Dental School by the X-Ray Department of the Naval Hospital and the X-Ray Equipment Research Division of the National Bureau of Standards, provides for a lead shield, permanently located or portable, with the timer located behind the shield in such a position that the operator is required to stand back of the shield in order to make the exposure. Such a shield, even if placed at 24 inches from the patient, would allow the operator to make 1500 full mouth sets of 14 exposures each per week and stay within the permissible dosage of 0.3 r.

Without a shield for protection, the permissible production of the operator drops greatly. For example, because each set of 14 exposures (41 seconds) would cause a technician standing from 36 to 44 inches away to receive 0.01 r, he would be allowed to take only 30 sets a week.

A comparison of the above two figures - 1500 sets of roentgenograms per week permissible with a lead shield, and only 30 sets per week without a shield - shows that a portable or permanent shield is indispensible to the technician for operating the dental x-ray room at capacity.

The portable screen is listed in the JAN Catalog as "Screen - X-ray Protective, #6-128-025."

Where a shield is not immediately available, or where the patient load is not large enough to require one, personnel making roentgenograms can be rotated and instructed to stand as far as possible from the patient during exposure time, and to work within the safe limits listed below.

Space surrounding the x-ray machine at the various dental activities varies considerably. The table below indicates safe distance-and-workload limits when a shield is not used; the distances given are from the patient to the operator at the time of exposure, and the seconds are in time alone and not in milliampere seconds:

At 24 inches a permissible 15 sets, 600 seconds per week.
At 35 inches a permissible 30 sets, 1200 seconds per week.
At 60 inches a permissible 50 sets, 2000 seconds per week.

Dental technicians should be appropriately instructed. The new Dental Technicians Handbook (General) now in preparation will include these revised permissible exposure standards. (Naval Dental School, NNMC, Bethesda, Md.)

Active Duty Naval Medical Officers: As of 1 November 1948, there were 2,524 medical officers on active duty in the Navy. Of these, 1,515 (60 percent) were of the regular Navy, and 1,009 (40 percent) were of the Naval Reserve. The following tables show the age, rank, board certifications, and specialties for USN and USNR:

USN AND USNR ACTIVE DUTY BY RANK AND AGE GROUP, AS OF 1 NOVEMBER 1948

RANK	TOTAL ALL AGES	AGE GROUP								
		20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60 & over
USN: Total	1,515	14	332	292	245	188	207	118	79	40
Rear Admiral	16	-	-	-	-	-	1	3	8	4
Captain	393	-	-	-	1	85	123	87	65	32
Commander	440	-	1	62	171	87	83	27	6	3
Lt. Commander	140	-	1	70	53	14	-	1	-	1
Lieutenant	166	-	23	125	16	2	-	-	-	-
Lieutenant (jg)	360	14	307	35	4	-	-	-	-	-
USNR: Total	1,009	49	826	67	10	12	11	16	15	3
Captain	23	-	-	-	-	1	2	3	14	3
Commander	28	-	-	3	4	6	7	8	-	-
Lt. Commander	26	-	-	10	4	5	1	2	1	-
Lieutenant	11	-	2	8	2	-	1	-	-	-
Lieutenant (jg)	921	49	824	46	2	-	-	-	-	-

CERTIFIED BY AMERICAN BOARDS AS OF 1 NOVEMBER 1948

FIRST AMERICAN BOARD	Number	% of Total
USN: Total	155	100.0
Dermatology and Syphilology	2	1.3
Internal Medicine	35	22.6
Obstetrics and Gynecology	14	9.0
Opthalmology	12	7.7
Orthopedic Surgery	1	0.6
Otolaryngology	20	12.9
Pathology	9	5.8
Pediatrics	9	5.8
Plastic Surgery	1	0.6
Psychiatry and Neurology	19	12.3
Radiology	16	10.3
Surgery	10	6.5
Urology	7	4.5
USNR: Total	6	100.0
Dermatology and Syphilology	1	16.7
Pathology	1	16.7
Psychiatry and Neurology	1	16.7
Surgery	3	50.0

BY SPECIALTY AS OF 1 NOVEMBER 1948

SPECIALTY	GRAND TOTAL	TOTAL USN	TOTAL USNR
Total	2,524	1,515	1,009
Medicine			
Aviation Medicine	306	228	78
Cardiovascular Diseases	3	3	-
Dermatology-Syphilology	21	20	1
Epidemiology	3	2	1
Gastro-Enterology	1	1	-
General Practice	1,275	388	887
Internal Medicine	172	165	7
Pathology, Clinical	28	25	3
Pathology, Tissue	18	17	1
Pediatrics	19	19	-
Public Health	21	21	-
Physical Therapy	5	4	1
Research	10	10	-
Radiology, Diagnostic	55	53	2
Tuberculosis	9	6	3
Tropical Medicine	3	3	-
Venereal Diseases	1	1	-
Neuropsychiatry			
Neuropsychiatry	13	12	1
Neurology	4	3	1
Psychiatry	47	41	6
Surgery			
Anesthesiology	12	10	2
Neurological Surgery	3	3	-
Obstetrics-Gynecology	80	75	5
Opthalmology	19	19	-
Opthalmic Surgery	3	3	-
Opthalmology-Otolaryngology	34	34	-
Otolaryngology	25	25	-
Orthopedics	41	40	1
Plastic Surgery	4	4	-
Surgery, General	233	224	9
Thoracic Surgery	1	1	-
Urology	55	55	-

(Statistics of Navy Medicine, Jan. '49)

Membership in the American College of Physicians: The following is taken from the latest information published by the American College of Physicians:

Proposal of Candidates Serving in the U. S. Navy. Any physician in the Medical Corps of the regular Navy shall be proposed and seconded for membership by separate Masters or Fellows in the College and endorsed by the Surgeon General in accordance with regulations already in effect.

Any physician in the U. S. Naval Reserve, on active duty, shall be presented for membership in the College in the same manner as a civilian physician; that is, he shall be proposed and seconded by Fellows of the College from his home state or territory where he formerly was in practice, and endorsed by the member of the Board of Governors from his home state or territory.

Five-Year Associate Term Extended in Case of Military Service. The maximum Associate term of five years, in the case of any Associate serving in the U. S. Navy during World War II, may be extended for a period commensurate in length with that on active duty, thus giving the said Associate adequate opportunity to meet the requirements for advancement to Fellowship. Each Associate who has served in the Public Services should establish, without delay, the date upon which his Associate term will expire and should take steps to submit his credentials for Fellowship at least sixty days in advance thereof.

Members of the American College of Physicians are of two classes: (1) Fellows, and (2) Masters.

(1) Fellows. Fellows shall be members of the medical profession engaged as practitioners, teachers, or research workers in internal medicine, or in an allied specialty, who shall have been elected in accordance with the By-Laws and such additional rules as the Board of Regents may from time to time adopt - the By-Laws and such additional rules being intended to insure the election only of internists of high qualifications, personal and professional.

Fellows shall be authorized to use the letters F.A.C.P. after their names on professional cards, in professional directories, and in professional publications.

(2) Masters. A special committee on Masterships will be named by the President of the College. This committee will consist of two members from the Board of Regents and one member from the Board of Governors. It will bring its nominations of Masters to the Board of Regents for election or rejection.

Requirements for Associateship. An Associate of the College shall have met the following qualifications and requirements:

(a) He shall hold the degree of M.D. from a medical school acceptable to the Board of Regents.

(b) After receiving his medical degree, the candidate shall have had at least one year of internship in an approved hospital and three years of organized graduate training in internal medicine or allied fields, or its equivalents, approved by the Committee on Credentials and the American Board of Internal Medicine. One year of this graduate training may be spent in the basic sciences.

(c) He shall be a member in good standing in his local, state, or territorial and national medical societies, except in the case of those not engaged in practice, such as full-time teachers, research workers, and those holding official hospital and similar positions.

(d) If a practitioner, he shall be licensed to practice medicine in his state, or territory, and shall indicate his purpose to confine his practice to internal medicine or an allied specialty from the date of his application, or be a medical officer in the Government Service. If not a practitioner, he shall hold an official institutional position in internal medicine, an allied branch of internal medicine, or in medical research.

Application for Associate Membership. Applicants for Associateship in the College shall be proposed in writing by a Master or Fellow of the College. A Master or Fellow of the College may be either a Naval medical officer or a civilian physician and not an officer or member of the Board of Regents of the College; each applicant shall be seconded by another Master or Fellow and his application submitted to the Bureau of Medicine and Surgery for review and an endorsement by the Surgeon General.

Requirements for Fellowship. A Fellow of the College shall have met the following qualifications and requirements:

(a) He shall have qualified and served a minimum period of three years as an Associate, except upon recommendation of the Committee on Credentials by reason of very special qualifications as hereinafter set forth.

(b) He shall have been graduated from a medical school acceptable to the Board of Regents, at least five years prior to the time of his election, and if engaged in practice, his professional activity must be confined to the field of internal medicine or a related specialty.

(c) If he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of internal medicine or an allied specialty

at a permanent location for at least three years preceding nomination for Fellowship. The Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify this ruling under exceptional conditions.

(d) The criteria of eligibility for election to Fellowship are bilateral:

1. Detailed information concerning the candidate's hospital and academic appointments, with particular reference to the size and nature of the hospital service and the exact teaching responsibility; published contributions in media acceptable to the Committee on Credentials, with particular emphasis upon papers published during the period of Associateship; personal approval by Fellows in his state or territory, with reference to his character, ethical standing and medical activities; evidence of postgraduate training and attendance upon the Annual Meetings of the College.

2. He shall be certified by the recognized national board of certification in his particular field, where such an accrediting board exists. This regulation, however, shall not apply to candidates from civilian life who were elected to Associateship prior to 6 April 1940, nor to such candidates from the U. S. Navy who were elected prior to and including 1 April 1944.

Application for Fellow Membership. Same procedure as for Associate Membership.

If further information should be desired regarding the American College of Physicians, please write to the Professional Division of the Bureau of Medicine and Surgery. (Professional Div., BuMed)

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Advanced Training for Staff Assignments: The Bureau of Naval Personnel has established a quota of medical and dental officers to be assigned to advanced training for ultimate assignments to logistic and staff billets as indicated below.

BuMed Quota	Convening Date	Reporting Date
INDUSTRIAL COLLEGE OF THE ARMED FORCES		
2 - MC	29 August 1949	25 August 1949
NAVAL WAR COLLEGE (SENIOR COURSE)		
1 - MC	12 August 1949	11 August 1949

BuMed Quota	Convening Date	Reporting Date
	NAVAL WAR COLLEGE (Cont.) (LOGISTICS COURSE)	
1 - MC	12 August 1949	11 August 1949
1 - DC	12 August 1949	11 August 1949
	ARMED FORCES STAFF COLLEGE	
2 - MC	September 1949	August 1949

Because the boards to select officers for these courses will be convened during February 1949, applications must reach BuMed prior to 1 February 1949 in order to receive consideration. Applications may be made by dispatch. No service agreement is required for these courses of instruction.

Attention is invited to BuPers Circular Letter 207-48 appearing on page 20, Navy Department Bulletin of 15 November 1948. (Professional Div., BuMed)

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Naval Medical Research Adviser Appointed: Dr. Howard T. Karsner, professor of pathology at Western Reserve University, Cleveland, Ohio, has been appointed Medical Research Adviser to the Surgeon General of the Navy and to the Director of the Research Division of the Navy Bureau of Medicine and Surgery.

As staff consultant, Doctor Karsner will assist and advise the Surgeon General, Rear Admiral C. A. Swanson, Medical Corps, U.S.N., concerning evaluation, coordination, and development of the Navy Medical Department's research program. (Office of Public Information, BuMed)

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Re Incandescent Lamps for Nasopharyngoscope: Stock Number 7-970-505 Lamp, Incandescent, Nasopharyngoscope: For nasopharyngoscope 3-482-500, will be deleted from the Army-Navy Catalog of Medical Materiel. Depot procurement and stocking of this item has proved impractical. Replacement bulbs for nasopharyngoscopes shall be the procurement responsibility of the activity concerned. Manufacturers of nasopharyngoscopes state that the "scopes" should be forwarded to the manufacturer for the fitting of bulbs. To avoid undue delay and inconvenience, MatDiv, BuMed recommends that when the instrument is forwarded to the manufacturer, at least 12 bulbs be ordered and fitted to the instrument prior to return. (Materiel Div., BuMed)

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Correction in Circular Letter: The following changes should be made in BuMed Circular Letter 48-128 as it appeared on page 32 of Medical News Letter of 17 December 1948:

In paragraph 2, change USNLV to USNEV.
In paragraph 7b, change USMEV to USNEV.

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Scientific Director of Medical Research at NMRI Appointed: Dr. Kenneth S. Cole, professor of biophysics at the University of Chicago, has been appointed as Technical Director of the Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland.

In his new assignment, Doctor Cole will be responsible for the policy and general direction of all fundamental research and scientific investigation at the Naval Medical Research Institute. The Institute's mission is to foster fundamental research in medicine and allied fields, and to make available the results of its investigations for the improvement of naval practice in the protection of personnel from injury, the prevention of disease, and treatment of the sick and injured. (Office of Public Information, BuMed)

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Meeting of Navy's Medical Consultants: The joint meeting of the Honorary and Reserve Consultants to the Navy's Bureau of Medicine and Surgery is planned for 28 and 29 January at the National Naval Medical Center, Bethesda, Maryland. The Honorary Consultants will assist in formulating future policies for the Medical Department of the Navy, and the Reserve Consultants will advise and evaluate the present graduate medical training program as well as the present status of the Medical Corps Reserve.

The Honorary Consultants, appointed by the Secretary of the Navy, act as an advisory board to the Surgeon General. The Reserve Consultants (mostly Naval Reserve officers), appointed by the Surgeon General, represent the specialties of the various specialty boards, and assist the Navy in establishing and maintaining a program which will provide training that meets the standards of these boards.

Consultants planning to attend:

Honorary	Reserve
Joseph L. T. Appleton, D.D.S.	Daniel F. Lynch, D.D.S.
Donald C. Balfour, M.D.	Marion Sulzberger, M.D.

Honorary

Edward LeRoy Bortz, M.D.
Sterling Bunnell, M.D.
Richard B. Cattell
Edwin J. Cohn, M.D.
Robert P. Fischelis, PharmD. ScD.
Evarts A. Graham, M.D.
Ernest Edward Irons, M.D.
Frank H. Lahey, M.D.
Oswald S. Lowsley, M.D.
Paul A. McNally, S.J.
Clyde E. Minges, D.D.S.
James E. Paullin, M.D.
Roscoe Lloyd Sensenich, M.D.
Charles Sheard, PhD.
Ernest L. Stebbins, M.D.
W. Calhoun Stirling, M.D.
Edward A. Strecker, M.D.
Meyer Wiener, M.D.
Philip E. Adams, D.M.D.

Reserve

J. Roscoe Miller, M.D.
Winchell M. Craig, M.D.
Paul Titus, M.D.
Arthur M. Culler, M.D.
Joseph S. Barr, M.D.
E. N. Broyles, M.D.
Shields Warren, M.D.
George M. Lyon, M.D.
Paul W. Greeley, M.D.
F. J. Braceland, M.D.
Wendell G. Scott, M.D.
Howard K. Gray, M.D.
M. G. Westmoreland, M.D.
Alphonse McMahon, M.D.
Donald Anderson, M.D.
Lowell T. Coggeshall, M.D.
Donald Hale, M.D.
A. C. Ivy, M.D.

(Office of Public Information, BuMed)

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Control of Use of Radioactive Isotopes: See Circular Letter 48-146 on page 34.

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BUMED CIRCULAR LETTER 48-142 13 December 1948

To: All Naval District and Staff Medical Officers

Subj: Training Program for Naval Reserve Hospital Corpsmen - Selection and Assignment of Regular Navy Chief Hospital Corpsmen to Duty at Naval Reserve Training Centers.

Refs: (a) BUMED C/L 47-31 dtd 13 Mar 1947.
(b) NavMed Form 1166 (Revised 9-47) "Outlines for Naval Reserve Curricula - Hospital Corps."
(c) BUMED C/L 47-99 dtd 4 Aug 1947.
(d) BUMED C/L 47-135 dtd 3 Oct. 1947.
(e) BUMED C/L 47-141 dtd 10 Oct 1947.
(f) BUMED C/L 47-173 dtd 15 Dec 1947.

This letter (1) states that the Navy Department has recently published enlisted personnel allowances authorizing the assignment of regular Navy Chief Hospital Corpsmen with Inspector-Instructors for duty at Naval Reserve Training Centers, including the training of Naval Reserve Hospital Corpsmen, (2) requests that special emphasis be placed upon this training program by all Medical Department officers concerned, following the organization and procedures in accordance with references (a) and (b), (3) establishes the qualifications desirable for selection of HMC's for this duty, (4) states that the tour of duty on these assignments will be for a maximum of three years and that it is assumed that this duty will be accompanied in most instances with subsistence allowances, (5) requests addressees to have each naval activity within their jurisdictions report the names of all HMC's on board who are considered qualified and recommended for this duty, and (6) directs that addressees forward to BuMed a brief quarterly progress report in duplicate letter form, showing the number of instructors assigned and the number of inactive Naval Reserve Hospital Corpsmen in both organized and volunteer groups under instruction.

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BUMED CIRCULAR LETTER 48-143 13 December 1948

To: All Ships and Stations

Subj: Requisitioning, Receipt Procedures, and Establishment of Stock Levels for Medical Stores

Refs: (a) BuMed Cir. Ltr. 48-73; N.D. Bul. of 30 June 1948, 48-470.
(b) BuMed Cir. Ltr. 48-24; N.D. Bul. of 29 February 1948, 48-117.

(c) Par. 23101, BuSandA Manual.
(d) Accounting Classification, Vol. VII, BuSandA Manual.

Encl: A (HW) Enclosure B (Revised 12-48) to BuMed Cir. Ltr. 48-73.

1. BuMed Cir. Ltr. 48-24 is hereby cancelled.

2. Enclosure B to reference (a) is hereby superseded by enclosure A of this letter.

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 48-144 14 December 1948

To: ComdtsNDs, Cont. U.S.; ComdrsNavTraCens; CONavTraSta; SuptUSNA; ComGensMarCorpsBases.

Subj: Tuberculin Testing, Navy and Marine Corps Personnel; Reporting of

Refs: (a) BuMed CL 47-91
(b) BuMed CL 48-6

This letter states that due to the paucity of reports received, in accordance with paragraph 2 of reference (a), activities addressed shall include in the Quarterly Sanitary Report for the period ending 31 Dec 1948 a summary of the results of tuberculin testing accomplished since institution of the program required by refs (a) and (b). The summary is to include the number of persons tested and the number of negative reactions, doubtful reactions, and +, ++, +++, ++++ reactions, respectively. This letter does not change the requirement that the results of tuberculin testing be included in each future Quarterly Sanitary Report of the activities addressed.

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BUMED CIRCULAR LETTER 48-145 14 December 1948

To: All Activities Under Management Control of the Bureau of Medicine and Surgery

Subj: Procedure for Accomplishment of Work Projects under the Specific Work Request Authorization

Refs: (a) BuMed Circular Letter No. 45-154.
(b) SecNav ltr - Ser1306/M610/CP:lhp, dtd 14 Oct 1947.

Encls: 1. (HW) Station Project Request.
2. (HW) Local Request for Estimate.
3. (HW) Check-Off List.

This letter cancels reference (a) and gives information and instructions concerning the procedures to be followed.

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BUMED CIRCULAR LETTER 48-146 16 December 1948

To: All Medical Department Activities

Subj: Use of Radioactive Isotopes; Control of

Refs: (a) BuMed ltr BUMED-3424-PV over NH/P3-3, dated 25 August 1947.
(b) BuMed Circular Letter 48-10.
(c) Manual of Radiological Safety (BuMed P-1283).

1. Reference (a) which lists certain requirements for the clinical use of isotopes and directs certain naval hospitals to establish isotope boards in accordance therewith is hereby cancelled and superseded by this directive.

2. Radioactive isotopes may not be used for any purpose in any naval medical installation without prior approval of the Bureau of Medicine and Surgery.

3. The Isotopes Division of the U. S. Atomic Energy Commission has stipulated that the hospital, or other institution, employing radioactive isotopes establish an "Isotope Committee" to evaluate proposals for isotope investigation within the institution and insure proper use of the materials. It is necessary to comply with this requirement and the committee formed in accordance therewith shall include:

(1) A physician trained in internal medicine.
(2) A physician trained in hematology.
(3) An individual experienced in assay of radiomaterials and protection of personnel against ionizing radiation.

Whenever possible, a qualified physicist and a therapeutic radiologist should be members of this committee or available in a consulting capacity. It is usually desirable to have a specially trained physicist to make the necessary measurements of materials and a radiochemist to perform other handling operations. Quite often one individual is qualified to carry out both of these functions.

4. It is necessary to set aside laboratory space for exclusive use in handling and storing radioisotopes. Similarly, a ward or rooms must be set aside for

the exclusive use of patients under treatment or investigation, to prevent any danger of widespread contamination. It is necessary to have on hand proper instruments for measuring the radiation dosages and for monitoring the areas in which the radioactive materials are used. The particular type of instrument employed will be dependent upon the isotope used. Information as to methodology can be found in references (b) and (c).

5. Procurement of radioactive isotopes and authority for use of same will be coordinated by BuMed, Code 74. Initial supply of the AEC forms to be used and other necessary information may be obtained from BuMed, Code 74, by those installations desiring to use radioisotopes.

6. For detailed information concerning organization and equipment of an isotope laboratory inquiry should be made to Radioisotopes Branch, Isotope Division, U. S. Atomic Energy Commission, Oak Ridge, Tennessee.

--BuMed. H. L. Pugh

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BUMED CIRCULAR LETTER 48-147 23 December 1948

To: All Medical Department Shore Activities

Subj: Report of Births to Fleet Hometown News Center, USNTC, Great Lakes, Illinois.

Ref: (a) BuMed Circ Ltr 47-101.

This letter (1) states that the Chief of Public Relations, Navy Department, has requested that all births in Naval Hospitals and Medical Department activities be reported in the form of a short story to Fleet Hometown News Center, USNTC, Great Lakes, Illinois, (2) directs addressees to comply, with a copy of report to BuMed, (3) outlines data required, and (4) states that this information is in addition to that required by reference (a).

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BUMED CIRCULAR LETTER 48-148 29 December 1948

To: All Ships and Stations

Subj: Heavy Dental Equipment; Standard Color for,

Ref: (a) BuMed Circular Letter No. 47-145 of 23 Oct 1947; AS&SL July-Dec. 1947, 47-1012, p. 244.

1. Change the color designation set forth in paragraph 1 of BuMed Circular Letter No. 47-145 from "Hue 2ca" to "Hue 2ec".

2. This color is known in the dental trade as "Cream white".

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 49-1 1 January 1949

To: All Activities with Medical Department Personnel Attached

Subj: NavMed-Fa, (Individual Report of Patient); Reporting of Surgical Operations on.

Ref: (a) Par. 236.3, MMD.

1. Effective upon receipt of this directive, Individual Statistical Report of Patient (NavMed-Fa) submitted to the Bureau shall include the titles of all operations or surgical procedures performed on the patient during the period covered by the report. These shall be on line 12 (Remarks) of the form, or, if additional space is required, on the back of the card. Surgical procedures performed for conditions other than the diagnosis shown in line 4 of the form shall be identified by being placed in parentheses.

2. An appropriate addition to the Manual of the Medical Department will be published at a later date.

--BuMed. C. A. Swanson

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